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By: /Julia L. Watts/ **Julia L. Watts** Date: June 8, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Claudia Cherney STEWART, et al.

Serial No.: 09/330,629

Filed: June 11, 1999

Art Unit: 1617

Examiner: San Ming R. Hui

Confirmation No.: 9658

Atty. Docket No.: JG-RP-4796/500561.20065

Customer No. 026418

METHOD OF HIV AND HPV PROPHYLAXIS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

This Brief is submitted in support of the Appeal filed January 8, 2007.

1. REAL PARTY IN INTEREST

The real party-in-interest is Redox Pharmaceutical Corporation, owner of all right and title and into the above-identified application, as evidenced by an assignment executed July 13, 1999, and recorded at Reel 010099 and Frame 0575.

2. RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, interferences or judicial proceedings known to the Appellant related to the above-identified application.

3. STATUS OF CLAIMS

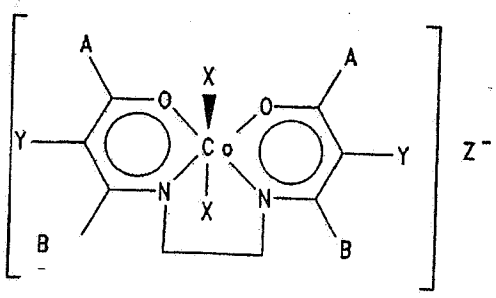
Claims 1-40 have been cancelled. Claims 41-53 were newly presented in a response filed June 27, 2005. The claims being appealed are Claims 41-53.

4. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final rejection.

5. SUMMARY OF THE CLAIMED SUBJECT MATTER

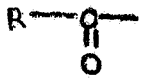
The present invention relates to a method for prophylactically reducing the risk of transmission of human immunodeficiency virus infection to a recipient and protecting the recipient from infection with human immunodeficiency virus infection by the typical application of an HIV infection prophylactic amount to a site on the recipient which is exposure to HIV of a composition comprising a compound having the structure:



(II)

wherein each

A is the same or different and is an alkyl group, a phenyl group or a substituted derivative of a phenyl group;

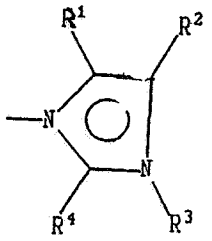
Y is the same or different and is hydrogen, an unbranched alkyl group, a halide or a group having the structure 

wherein R is hydrogen, an alkoxide group, an alkyl group, or OH;

B is the same or different and each is hydrogen or an alkyl group;

Z^- is a soluble, pharmaceutically acceptable negative ion; and

X is the same or different and is an axial ligand selected from the group consisting of moieties having the formula:



(IIa)

wherein R^1, R^2, R^3, and R^4 are the same or different and may be hydrogen or lower alkyl having from 1 to 4 carbon atoms;

with the proviso that R^1, R^2, R^3, and R^4 are of a sufficiently small size so as not to prohibit the attachment of the axial ligand to the Co atom due to steric hindrance.

In particular, the Applicant has discovered upon application of an HIV affective of the recited compound, the virus can be prohibited from entering the potential host. This is a surprising result and is amply demonstrated in the data within the application.

6. THE GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

ISSUE 1: Whether Claims 41-53 are unpatentable under 35 U.S.C. §103(a) over Dori WO 93/11140 in view of Cooper, et al. U.S. Patent 4,242,359 and Field's (Virology) pages 26-27, Lippincott-Raven, 1996, and the Merck Manual 16th Ed., 1992, pages 49-55.

It is noted that the Examiner raised a provisional obviousness-type double-patenting rejection over Application Serial No. 10/662,848. However, this application has not been patented and therefore the rejection remains provisional. When that application issues as a patent, Applicants plan to file a terminal disclaimer to obviate the obviousness-type double patenting rejection.

7. ARGUMENT

The Examiner has asserted that Dori teaches a method of treating viral infection and decreasing viral titer broadly by topical administration of the metallo-organic cobalt compounds including specific compound 96 of the present specification. The Examiner recognizes that Dori does not expressly teach a method of prophylaxis for HIV infection by topical administration of the compound. Also, Dori does not expressly teach the method of using a condom as an applicator to topically apply the compound.

The Examiner relies on Cooper, et al. as teaching a method for topical administration of the medical agent by applicators which include a condom. Field is relied on as teaching the common viral pathogens in humans, referring to Table 4, pages 26-27 and the Examiner relies on the Merck Manual as teaching the employing of anti-infective agents (both anti-viral and anti-bacterial) in anti-microbial chemo-prophylaxis as common practice in the pharmaceutical field referring to pages 49-55. The Examiner has concluded that it would have been obvious for one of ordinary skill in this art at the time the invention was made to topically administer the compound recited in the claims to a site on the subject for prophylaxis of HIV infection. The Examiner bases this proposition on the assertion that the Dori compounds are known to be effective in treating viral infections and decreasing vital titer broadly and it would be reasonable to expect the same compounds, including compounds known as Compound

96 to be useful in prophylaxis or reduction of the incidences of any viral infection including those called by HIV strains.

It is submitted that the claims on appeal are not rendered obvious by this combination of references relied on by the Examiner. Also, it is submitted that the Examiner's description of the references is an improper characterization. The present application and claims refer to prophylaxis. This means that a drug is used which interacts with the virus outside of the cell prior to its entry and which prevents the virus from entering the cell and initiating an infection. Compound CTC-96 achieves this with both HIV and HSV. Most drugs against these and other viruses act on virus replication once it is already inside the cell. Examples are Acyclovir and related drugs that do not interact with the intact virus and thus cannot prevent its entry into the cell.

As shown by the Schwartz, et al. article in the Journal of Virology submitted to the Examiner, CTC-96 prevents the virus from interacting with the cell, i.e., from entering the cell. It exhibits a broad spectrum of such activity on enveloped viruses, such as, HIV. None of the nucleotide analogues, such as Acyclovir, will do that. They are therapeutic, i.e., act on the virus after it has infected the cell and are not prophylactic as is CTC-96.

The articles submitted support the fact that the invention as recited in the claims with respect to the compounds referred to therein do exert a prophylactic effect by acting on the virus outside the cell.

In the Advisory Action, the Examiner argued that the reasons submitted by the Applicants are predicated on the fact that not all drugs are effective in treating HIV or will inhibit the entry of HIV into the cells and therefore not every anti-HIV drug will be useful in the prophylaxis of HIV even though the drugs are effective in treating HIV. The Examiner disagrees with this logic on the ground that the prophylaxis of HIV does not necessarily inhibit the viral entry to the cells. The Examiner argues it can also be done on the basis of inhibiting the first replication of the virus once it gets into the cell and thereby inhibit or reduce the chance of HIV manifestation in the patients. The Examiner further argues that the claimed compounds can lower the viral titer and are known to be useful in treating viral infection, and therefore it would be reasonably expected to be useful in lowering the viral titer and thereby reducing the chance of HIV infection.

However, this begs the question because the viral titer is measured once the cell has been infected. A person skilled in this art understands the fact that a compound may have a therapeutic effect in treating a virus that has entered into the cells of a subject, yet have no relationship to the properties that the compound may exhibit with respect to a virus that has not yet entered the subject. The form of the virus that is within the host is different from the form of the virus before it has infected the host. Consequently, the fact that the drug might be effective against the form of the virus after infection is in no way indicative that it may be effective against the form of the virus prior to the infection. The references do not disclose the use of these compounds for the prevention of HIV or HSV.

It is well known that the viral life-cycle is complex and consists of a number of distinct stages, including cellular adhesion and viral entry, replication of viral nucleic acid, synthesis of viral proteins, assembly and cellular exit of viral particles (see, for example, the enclosed excerpts from Smith, et al. 2003, *Science*, 304:237 and Brock, et al., *Biology of Microorganisms*, 6th Edition 1991, Prentice Hall, pgs 189-190.)

Each stage is a potential target for regulating the viral life-cycle by anti-viral agents – preventing certain stages in the viral life-cycle may stop the continued generation of viral particles within a cell, i.e., a pre-existing viral infection, while preventing other stages may stop the initial steps of viral infection of an uninfected cell, i.e., preventing a viral infection.

For example, as evidenced by the Doms, et al. article (2004, *N. Engl. J. Med.*, 351:743-4) and in particular page 743, lines 1-15, a new class of agents that block the entry of a virus into the cell has recently been developed which therefore have application in preventing viral infection, in addition to existing drugs that inhibit viral enzymes within the host cell and which therefore prevent post-infection replication of the virus.

Contrary to the Examiner's allegations, it is not necessarily the case that a compound which is capable of treating an existing viral infection will also be capable of preventing a viral infection. For example, nucleoside analogs such as Acyclovir and AZT are capable of preventing viral replication, but have no effect on viral entry.

In Fields, et al. (2002, *Virology* 4th Edition, Vol. 1, Chapter 15, pages 394-395), Acyclovir is an analog of guanosine, which enters the cell like other nucleotides. It is activated by a specific herpes virus enzyme, thymidine kinase, which is released inside the cell following penetration of the virus. The phosphorolated Acyclovir molecules then inhibit viral DNA polymerase and thus stop viral DNA replication. Accordingly, Acyclovir will have no effect on the entry of the virus into the host cell.

As further discussed in Fields, et al. (2020, Virology 4th Edition, Vol. 1, Chapter 15, page 404-405), AZT is a drug widely used against HIV, which is a synthetic pyrimideine analog that binds with great avidity to the reverse transcriptase of human immunodeficiency virus. When the virus is inside the cell and starts the phase of the replication of the viral nucleic acid, since AZT can only act after is phosphyorolated inside the cell, it has no effect on extracellular viral particles, or the mechanism of entry into a host cell.

There is clearly no teaching or suggestion in the art relied on by the Examiner of the molecular mechanism underlying the observed anti-viral effect of the compound shown herein or the stage in the viral life cycle at which those compounds function. Consequently, even if a skilled person were to use the compounds prophylactically, which they would have no reason to do, there could be no reasonable expectation that such an approach would be successful since as noted above, one with ordinary skill in this art would not know whether those compounds acted on a stage of the viral life-cycle that would result in prevention of viral infection.

The Schwartz, et al. article in the *Journal of Virology* show that it is known that compounds of the class presently claimed exert their anti-viral effect by inhibiting entry of the envelope virus into host cells, but have no effect on the accumulation of viral proteins after initiation of infection (see, for example, page 4120 of Schwartz, et al.). Accordingly, compounds of the invention can be used prophylactically, i.e. to prevent viral infection. However, while the mechanism is now known, it was not known on June 11, 1999, the priority date of the present application, nor is it in any way taught or suggested in D1 or the combination of references. Consequently, it would not have been obvious to use this compound prophylactically as recited in the present claims.

Indeed, in view of the significant and on-going need to develop effective vaccines and prophylactic treatment for herpes virus infections, we submit that had it been obvious to use the compounds of the Dori reference prophylactically, it would have been done within the five (5) year period between the publication of that reference and the filing date of the present application. Five (5) years represents a significant period in any area of biological research, and in particularly, in the field of medicine where there is strong pressure to develop commercially valuable drugs to reduce patient suffering.

As previously noted, the form of the virus that is within the host is different from the form of the virus before it has infected the host and there is nothing in this art which remotely suggests that this compound would be effective against the form of the virus before it has infected the host. This rejection should not be sustained.

8. CONCLUSION

In view of the foregoing, it is submitted that the claims on appeal are allowable over the art relied on by the Examiner and this Board is respectfully requested to reverse the decision of the Examiner.

Respectfully submitted,

Dated: June 8, 2007

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